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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/944,849	08/31/2001	Brian J. Nickoloff	212583	4478

23460 7590 08/26/2003

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	18

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/944,849	NICKOLOFF ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 18-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-53* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Note that claim 4 was inadvertently added to Group II, which requires "providing extracellularly a Notch agonist" (see definition of Group II on page 2 of previous Office action). Inclusion of claim 4 was an obvious error since it requires "at least one Notch agonist... provided to the at least one epithelial cell intracellularly." This claim belongs only with Group I and not Group II.

Applicant's election with traverse of Group II, species of Notch agonist as consisting essentially of SEQ ID NO:10, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that there would be no serious search burden for examination of more than one invention. This is not found persuasive because as previously stated, the methods require different method steps and different substances, which substances are themselves different. These differences necessitate unique searches for each group and it is maintained that searching for more than one invention would be burdensome for the above reasons and those previously stated in the restriction of paper # 8. Additionally, the burden of search for the Office has increased with multiple sequences because of the rapid introduction of new sequences to public sequence databases.

Claims 4, 5 and 18-53 are withdrawn from consideration, as are species recited in claims 1-3 and 6-17 which are not elected.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The disclosure is objected to because of the following informalities: on page 40, line 37, "lies" should be "lines".

Appropriate correction is required.

Claim Objections

Claims 1-3 and 6-17 are objected to for including non-elected species.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7-9 and dependent claims 2, 3 and 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of claims 7-9 cannot be determined in view of the term "derivative". It is unclear if, for example, SEQ ID NO:11 and 12 are derivatives of SEQ ID NO:10. Note that SEQ ID NO:11 and 12 are not elected species and will not be examined here. The specification describes fragments or derivatives as altered, truncated or augmented sequences. There is no limiting definition of a derivative or an altered sequence. How much alteration may occur such that the protein is still considered a derivative is not clear.

Claim 1 is indefinite because it is unclear if the 3 references to "at least one epithelial cell" in lines 3 and 4 refer to the original "at least one epithelial cell" in line one of the preamble of the claim or to a different epithelial cell. This rejection could be obviated by replacing the 3 later references with "said at least one epithelial cell".

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 6-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The elected invention is drawn to using SEQ ID NO:10 to induce differentiation of epithelial cells. According to the specification on page 6, lines 26-28, SEQ ID NO:10 (JAG-1c) is derived from the Delta/Serrate/LAG-2 (DSL) domain of hJagged1 (human Jagged1). SEQ ID

NO:10 corresponds to amino acids 188-207 of hJagged-1 protein (SEQ ID NO:3), but has 3 amino acids which are different (amino acid 1, 8 and 12 of SEQ ID NO:10). SEQ ID NO:11, referred to as JAG-1 corresponds exactly to residues 188-204 of hJagged-1 (p. 30, lines10-12). The working examples of the present invention used JAG-1 which differs from JAG-1c by being 4 amino acids shorter and having 3 different corresponding amino acids. As to fragments of SEQ ID NO:10, neither the prior art nor specification support a reasonably expectation that fragments smaller than at least amino acids 188-204 of hJagged-1 could function to induce differentiation. While testing could be done to determine the minimum size, there is no guidance in the specification to allow the skilled artisan to know what the minimum size is without first conducting critical experiments.

The question of derivatives is discussed above in the rejection under 35 USC 112, second paragraph, because it is unclear from the specification what is considered a derivative of SEQ ID NO:10. Clearly from the working examples present in the instant application SEQ ID NO:11 functions to induce differentiation of epidermal cells. There is no guidance for predicting which amino acids could be altered from SEQ ID NO:11 while still providing a protein with the necessary function, this includes predicting whether the 3 amino acids that differ between SEQ ID NO:10 and 11 would affect function as required by the claims. Nor could it be determined how many amino acids could be added to either end of SEQ ID NO:10 while maintaining function without significant further experimentation.

The claims also encompass proteins consisting essentially of SEQ ID NO:10. In MPEP 2111.03, "A consisting essentially of" claim occupies a middle ground between closed claims that are written in a "consisting of" format and fully open claims that are drafted in a "comprising" format." PPG Industries v.Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir.1998). According to this, if SEQ ID NO:10 was a fragment of human Jagged-1, then consisting essentially of SEQ ID NO:10 could encompass any size fragment of hJagged-1 comprising SEQ ID NO:10. However, as discussed above, SEQ ID NO:10 is not a fragment of human Jagged-1. Therefore, the analysis of "consisting essentially of" language and "derivative" in the claims are equivalent. As previously discussed, it is unpredictable with the information provided by the prior art and specification what effect additions or changes to SEQ ID NO:10 would result without significant further experimentation. The use of the terms

"consisting essentially of" and "derivative" provide an invitation to experiment without a reasonable expectation of which changes would result in a protein having the necessary claimed function.

Further, even if SEQ ID NO:10 were enabled for inducing differentiation of epithelial cells, which it is not, it would not be enabled for using the full scope of the broad class of epithelial cells. Epithelial cells are found in diverse locations within the body, forming skin as well as lining vessels and covering and lining glands and organs. The role of Jagged-1 in the formation or differentiation of these cells was not well understood in the prior art, though its presence had been detected in a variety of endothelial cells (*e.g.*, last paragraph of page 788 of Gray et al., Am. J. Pathol., 154:785-794, 1999, reference AW cited by Applicants). Further Zimrin et al. in WO 97/45143 (p. 42, lines 3-9) found a complex and unpredictable action of Jagged in experiments:

> When viewed together, these results indicated Jagged-Notch signaling as an *anti*-migratory event in the endothelium comprising the microvasculature, but as a *pro*-migratory event in the endothelium of large vessels. These experiments demonstrated for the first time that there apparently exists a major phenotype difference between small and large vessel endothelial cells in response to a ligand-receptor signaling pathway in the endothelial cell which is modulated during the migratory phase of angiogenesis.

Additionally, Li et al. (Immunity, 8:43-55, 1998) show results that do not support the general role of Jagged-1 in differentiation (p. 44, second full paragraph). They found that human Jagged1 was expressed by a subpopulation of cells in bone marrow and the representative human stromal cell line HS-27a. However, this cell line promoted proliferation and survival but inhibited granulocyte differentiation of full-length Notch-1 (the receptor for Jagged-1) expressing 32D cells. "In addition, we show that conditioned medium from COS cells expressing a secreted extracellular hJagged1 protein and a peptide corresponding to the DSL domain of hJagged1 have the same functional effects in this system."

What the instant specification shows in a number or experiments is that a polypeptide called JAG-1 and having the sequence of SEQ ID NO:**11** causes differentiation of **epidermal** epithelial cells. Experiments show that keratinocytes undergo corneogenesis. There are no working examples of differentiation of other epithelial cells. The prior art shows that the function of Jagged-1 on epithelial cells is unpredictable, and depends at least on the type of

epithelial cell if not also on the developmental stage of the cells. The prior art has conflicting results about the role of Notch in inducing differentiation of epithelial stem cells when the Notch pathway is activated. For example, US Patent 6,149,902 (AM, cited by Applicants) suggests in the discussion in section 5 (col. 14-24) that the action of Notch agonists is to induce differentiation of stem cells, though there are no actual experiments to support the assertion. Also, US Patent 6,337,387 shows that the extracellular domain, which includes the DSL domain, of either human Delta-1 and Serrate-1 (also called Jagged1) fused to an Ig domain to make a chimeric protein, caused suppression of colony formation in undifferentiated blood cells (*e.g.*, col. 30, lines 55-66).

The specification provides an invitation for experimentation to determine the effect of SEQ ID NO:10 epithelial cells and fails to provide direction or guidance that would lead the skilled artisan to reasonably expect successful induction of differentiation of all or any specific non-epidermal type of or non-stem cell type of epithelial cell even for SEQ ID NO:11, the peptide used in the experiments of the specification but a non-elected species. For these reasons, one could not practice the method as claimed as it relates broadly to epithelial cells without undue experimentation.

For claims 11-13, the methods include gene therapy with expression of the agonist by a cell in a patient/subject. This expression by gene therapy is extremely unpredictable and has no support in the prior art for wide application of the method. There is no showing in the specification that integration into appropriate cells' transcription pathway or translation of a nucleic acid encoding SEQ ID NO:10 would be possible within a cell in an animal. There are examples in the specification using JAG-1 (SEQ ID NO:11) added as a peptide **extracellularly.** There is insufficient guidance to allow the skilled artisan to practice the method by the manner claimed with a reasonable expectation of success and without undue experimentation.

For the reasons set forth above, which include the breadth of the claims and lack of direction or guidance as they relate to derivatives of SEQ ID NO:1 and type of epithelial cells, the unpredictability of the action of SEQ ID NO:10 on a Notch receptor/pathway, the lack of working examples using JAG-1c of SEQ ID NO:1 to induce differentiation of an epithelial cell and the limited knowledge and complex findings of the prior art, it would require undue experimentation to practice the invention as claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

August 22, 2003